

What is claimed is:

1. A chimeric fibroblast growth factor (FGF), comprising:
 - a. a biologically active fibroblast growth factor (FGF) protein having a first amino acid sequence; and,
 - b. a penetratin peptide having a second amino acid sequence, wherein said penetratin peptide transports said chimeric fibroblast growth factor (FGF) across a lipid bilayer of a cell independently of the presence of an FGF receptor, wherein said second amino acid sequence is linked to said first amino acid sequence; wherein said chimeric fibroblast growth factor (FGF) is characterized by:
 - (i) fibroblast growth factor (FGF) biological activity in the absence of heparan sulfate; and,
 - (ii) entry into a living cell in the absence of a receptor that binds to FGF.
2. The chimeric fibroblast growth factor (FGF) of Claim 1, wherein said FGF biological activity is characterized by:
 - a. repression of terminal differentiation in the absence of heparan sulfate; and,
 - b. promotion of cell proliferation in the absence of heparan sulfate.
3. The chimeric fibroblast growth factor (FGF) of Claim 1, wherein said second amino acid sequence is linked to the N-terminus of said first amino acid sequence.
4. The chimeric fibroblast growth factor (FGF) of Claim 1, wherein said FGF protein is encoded by a nucleic acid molecule that hybridizes under stringent hybridization conditions to a nucleic acid molecule encoding a protein selected from the group consisting of fibroblast growth factor-1 (FGF-1) protein and fibroblast growth factor-2 (FGF-2) protein, wherein said FGF protein has FGF biological activity.
5. The chimeric fibroblast growth factor (FGF) of Claim 1, wherein said FGF protein is selected from the group consisting of a fibroblast growth factor-1 (FGF-1) protein and a fibroblast growth factor-2 (FGF-2) protein.

6. The chimeric fibroblast growth factor (FGF) of Claim 1, wherein said FGF protein comprises an amino acid sequence selected from the group consisting of SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7 and SEQ ID NO:8.

7. The chimeric fibroblast growth factor (FGF) of Claim 1, wherein said FGF protein is a fibroblast growth factor-2 protein.

8. The chimeric fibroblast growth factor (FGF) of Claim 1, wherein said FGF protein has an amino acid sequence comprising from position 18 through position 172 of SEQ ID NO:2 or from position 17 through 171 of SEQ ID NO:4.

9. The chimeric fibroblast growth factor (FGF) of Claim 1, wherein said penetratin peptide is selected from the group consisting of:

a. a first peptide having an amino acid sequence selected from the group consisting of:

(i) $X_1-X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12}-X_{13}-X_{14}-X_{15}-X_{16}$;

and,

(ii) $X_{16}-X_{15}-X_{14}-X_{13}-X_{12}-X_{11}-X_{10}-X_9-X_8-X_7-X_6-X_5-X_4-X_3-X_2-X_1$;

wherein $X_1, X_2, X_3, X_4, X_5, X_7, X_8, X_9, X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, X_{15}$, and X_{16} each represent an α -amino acid, between 6 and 10 of which are hydrophobic amino acids; and wherein X_6 represents Trp; and,

b. a second peptide comprising amino acid residues 49-57 of HIV Tat protein (SEQ ID NO:17).

10. The chimeric fibroblast growth factor (FGF) protein of Claim 9, wherein said second peptide does not comprise amino acid residues 22-36 or 73-86 of HIV Tat protein (SEQ ID NO:17).

11. The chimeric fibroblast growth factor (FGF) of Claim 9, wherein said first peptide is selected from the group consisting of a peptide comprising helix 3 of a homeobox domain and a homeobox domain.

12. The chimeric fibroblast growth factor (FGF) of Claim 9, wherein said first peptide comprises an amino acid sequence selected from the group consisting of SEQ ID

NO:9, amino acid residues 42 through 58 of SEQ ID NO:9, amino acid residues 43 through 59 of SEQ ID NO:9, amino acid residues 43 through 58 of SEQ ID NO:9, amino acid residues 58 through 43 of SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, and SEQ ID NO:16.

13. The chimeric fibroblast growth factor (FGF) of Claim 9, wherein said first peptide comprises amino acid residues 2-17 of SEQ ID NO:2.

14. The chimeric fibroblast growth factor (FGF) of Claim 9, wherein said second peptide comprises an amino acid sequence from an HIV Tat protein selected from the group consisting of amino acid residues 37-72 of SEQ ID NO:17, amino acid residues 38-72 of SEQ ID NO:17, amino acid residues 47-72 of SEQ ID NO:17, amino acid residues 37-58 of SEQ ID NO:17, amino acid residues 38-58 of SEQ ID NO:17, amino acid residues 47-58 of SEQ ID NO:17, amino acid residues 1-21 and 38-72 of SEQ ID NO:17, amino acid residues 47-62 of SEQ ID NO:17, amino acid residues 38-62 of SEQ ID NO:17, amino acid residues 1-72 of SEQ ID NO:17, amino acid residues 1-58 of SEQ ID NO:17, and amino acid residues 48-60 of SEQ ID NO:17.

15. The chimeric fibroblast growth factor (FGF) of Claim 9, wherein said second peptide comprises amino acid residues 48-60 of SEQ ID NO:17 or amino acid residues 2-14 of SEQ ID NO:4.

16. The chimeric fibroblast growth factor (FGF) of Claim 1, wherein said chimeric fibroblast growth factor (FGF) comprises an amino acid sequence selected from the group consisting of SEQ ID NO:2 (HLX-FGF) and SEQ ID NO:4 (TAT-FGF).

17. The chimeric fibroblast growth factor (FGF) of Claim 1, wherein said chimeric fibroblast growth factor (FGF) is encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO:1 (HLX-FGF) and SEQ ID NO:3 (TAT-FGF).

18. A therapeutic composition comprising the chimeric fibroblast growth factor (FGF) of Claim 1 and a pharmaceutically acceptable excipient.

19. A recombinant nucleic acid molecule encoding a chimeric fibroblast growth factor (FGF), comprising:

a. a first isolated nucleic acid sequence encoding a biologically active fibroblast growth factor (FGF) protein; and,

b. a second isolated nucleic acid sequence encoding a penetratin peptide that transports said chimeric fibroblast growth factor (FGF) across a lipid bilayer of a cell independently of the presence of an FGF receptor, wherein said second nucleic acid sequence is linked to said first nucleic acid sequence;

wherein said first and second nucleic acid sequences are operatively linked to a transcription control sequence; and,

wherein said chimeric fibroblast growth factor (FGF) is characterized by:

(i) fibroblast growth factor biological activity in the absence of heparan sulfate; and,

(ii) entry into a living cell in the absence of a receptor that binds to FGF.

20. The recombinant nucleic acid molecule of Claim 20, wherein said fibroblast growth factor biological activity is characterized by:

a. repression of terminal differentiation in the absence of heparan sulfate; and,

b. promotion of cell proliferation in the absence of heparan sulfate.

21. The recombinant nucleic acid molecule of Claim 20, wherein said first nucleic acid sequence hybridizes under stringent hybridization conditions to a nucleic acid molecule encoding an FGF protein selected from the group consisting of a fibroblast growth factor-1 (FGF-1) protein and a fibroblast growth factor-2 (FGF-2) protein, wherein said FGF protein has FGF biological activity.

22. The recombinant nucleic acid molecule of Claim 20, wherein said first nucleic acid sequence encodes an FGF protein selected from the group consisting of a fibroblast growth factor-1 (FGF-1) protein and a fibroblast growth factor-2 (FGF-2) protein.

23. The recombinant nucleic acid molecule of Claim 20, wherein said first nucleic acid sequence encodes an FGF protein comprising an amino acid sequence selected from the group consisting of SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7 and SEQ ID NO:8.

24. The recombinant nucleic acid molecule of Claim 20, wherein said first nucleic acid sequence encodes a fibroblast growth factor-2 protein.

25. The recombinant nucleic acid molecule of Claim 20, wherein said first nucleic acid sequence comprises from nucleotide 59 to 523 of SEQ ID NO:1 or from nucleotide 59 to 523 of SEQ ID NO:3.

26. The recombinant nucleic acid molecule of Claim 20, wherein said second nucleic acid sequence encodes a penetratin peptide selected from the group consisting of:

a. a first peptide having an amino acid sequence selected from the group consisting of:

(i) $X_1-X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12}-X_{13}-X_{14}-X_{15}-X_{16}$;

and,

(ii) $X_{16}-X_{15}-X_{14}-X_{13}-X_{12}-X_{11}-X_{10}-X_9-X_8-X_7-X_6-X_5-X_4-X_3-X_2-X_1$;

wherein $X_1, X_2, X_3, X_4, X_5, X_7, X_8, X_9, X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, X_{15}$, and X_{16} each represent an α -amino acid, between 6 and 10 of which are hydrophobic amino acids; and wherein X_6 represents Trp; and,

b. a second peptide comprising amino acid residues 49-57 of HIV Tat protein (SEQ ID NO:17).

27. The recombinant nucleic acid molecule of Claim 27, wherein said peptide does not comprise amino acid residues 22-36 or 73-86 of HIV Tat protein (SEQ ID NO:17).

28. The recombinant nucleic acid molecule of Claim 27, wherein said first peptide is selected from the group consisting of a peptide comprising helix 3 of a homeobox domain and a homeobox domain.

29. The recombinant nucleic acid molecule of Claim 27, wherein said first peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO:9, amino acid residues 42 through 58 of SEQ ID NO:9, amino acid residues 43 through 59 of

5 SEQ ID NO:9, amino acid residues 43 through 58 of SEQ ID NO:9, amino acid residues 58 through 43 of SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, and SEQ ID NO:16.

5 30. The recombinant nucleic acid molecule of Claim 27, wherein said second peptide comprises an amino acid sequence from an HIV Tat protein selected from the group consisting of amino acid residues 37-72 of SEQ ID NO:17, amino acid residues 38-72 of SEQ ID NO:17, amino acid residues 47-72 of SEQ ID NO:17, amino acid residues 37-58 of SEQ ID NO:17, amino acid residues 38-58 of SEQ ID NO:17, amino acid residues 47-58 of SEQ ID NO:17, amino acid residues 1-21 and 38-72 of SEQ ID NO:17, amino acid residues 47-62 of SEQ ID NO:17, amino acid residues 38-62 of SEQ ID NO:17, amino acid residues 1-72 of SEQ ID NO:17, amino acid residues 1-58 of SEQ ID NO:17, and amino acid residues 48-60 of SEQ ID NO:17.

31. The recombinant nucleic acid molecule of Claim 27, wherein said second nucleic acid sequence comprises nucleotides 11 to 58 of SEQ ID NO:1.

32. The recombinant nucleic acid molecule of Claim 27, wherein said second nucleic acid sequence comprises residues 14 to 52 of SEQ ID NO:3.

33. The recombinant nucleic acid molecule of Claim 20, wherein said recombinant nucleic acid molecule comprises a nucleic acid sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:3.

34. The recombinant nucleic acid molecule of Claim 20, wherein said recombinant nucleic acid molecule comprises a nucleic acid sequence encoding an amino acid sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:4.

35. A recombinant cell that expresses the recombinant nucleic acid molecule of Claim 20.

36. A recombinant virus comprising the recombinant nucleic acid molecule of Claim 20.

37. A method to produce a chimeric fibroblast growth factor (FGF), comprising culturing in an effective medium a recombinant cell comprising a recombinant nucleic acid molecule encoding a chimeric fibroblast growth factor protein, said recombinant nucleic acid molecule comprising:

- 5 a. a first isolated nucleic acid sequence encoding a biologically active fibroblast growth factor (FGF) protein; and,
- 10 b. a second isolated nucleic acid sequence encoding a penetratin peptide that transports said chimeric fibroblast growth factor (FGF) across a lipid bilayer of a cell independently of the presence of an FGF receptor, wherein said second nucleic acid sequence is linked to said first nucleic acid sequence;
- wherein said first and second nucleic acid sequences are operatively linked to a transcription control sequence; and,
- wherein said chimeric fibroblast growth factor (FGF) is characterized by:
- (i) fibroblast growth factor biological activity in the absence of
- 15 heparan sulfate; and,
- (ii) entry into a living cell in the absence of a receptor that binds to FGF;
- wherein said recombinant cell expresses said chimeric fibroblast growth factor (FGF).

38. A method to repress terminal differentiation and promote proliferation in a cell, comprising administering to a cell a chimeric fibroblast growth factor (FGF) protein comprising:

a. a biologically active fibroblast growth factor (FGF) protein having a first amino acid sequence; and,

b. a penetratin peptide having a second amino acid sequence, wherein said penetratin peptide transports said chimeric fibroblast growth factor (FGF) across a lipid bilayer of a cell independently of the presence of an FGF receptor, wherein said second amino acid sequence is linked to said first amino acid sequence;

wherein said chimeric fibroblast growth factor (FGF) is characterized by:

(i) fibroblast growth factor biological activity in the absence of heparan sulfate; and,

(ii) entry into a living cell in the absence of a receptor that binds to FGF.

39. The method of Claim 39, wherein said cell has reduced heparan sulfate proteoglycan production characterized by a reduction in both repression of terminal differentiation and promotion of proliferation in the presence of naturally occurring fibroblast growth factor.

40. The method of Claim 39, wherein said cell is a cell of patient that has a condition selected from the group consisting of stroke, nerve damage, bone damage, muscle damage, and a wound.

41. The method of Claim 39, wherein said chimeric fibroblast growth factor (FGF) is administered to said cell *in vivo*.

42. A method to enhance a biological process selected from the group consisting of mitogenesis, angiogenesis, wound healing, neurogenesis, limb patterning, limb outgrowth, comprising administering to cells associated with said biological process a chimeric fibroblast growth factor (FGF) comprising:

a. a biologically active fibroblast growth factor (FGF) protein having a first amino acid sequence; and,

b. a penetratin peptide having a second amino acid sequence, wherein said penetratin peptide transports said chimeric fibroblast growth factor (FGF) across a lipid bilayer of a cell independently of the presence of an FGF receptor, wherein said second amino acid sequence is linked to said first amino acid sequence; wherein said chimeric fibroblast growth factor (FGF) is characterized by:

(i) fibroblast growth factor biological activity in the absence of heparan sulfate; and,

(ii) entry into a living cell in the absence of a receptor that binds to FGF.

5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
105
110
115
120
125
130
135
140
145
150
155
160
165
170
175
180
185
190
195
200
205
210
215
220
225
230
235
240
245
250
255
260
265
270
275
280
285
290
295
300
305
310
315
320
325
330
335
340
345
350
355
360
365
370
375
380
385
390
395
400
405
410
415
420
425
430
435
440
445
450
455
460
465
470
475
480
485
490
495
500
505
510
515
520
525
530
535
540
545
550
555
560
565
570
575
580
585
590
595
600
605
610
615
620
625
630
635
640
645
650
655
660
665
670
675
680
685
690
695
700
705
710
715
720
725
730
735
740
745
750
755
760
765
770
775
780
785
790
795
800
805
810
815
820
825
830
835
840
845
850
855
860
865
870
875
880
885
890
895
900
905
910
915
920
925
930
935
940
945
950
955
960
965
970
975
980
985
990
995